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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/817,704	08/25/97	SWAAK	A P8214-7002

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NIKAIDO MARMELSTEIN MURRAY & ORAM
METROPOLITAN SQUARE
655 15TH STREET WN
SUITE 330 G STREET LOBBY
WASHINGTON DC 20005-5701

EXAMINER	
CUNNINGHAM, T	
ART UNIT	**PAPER NUMBER**
1644	15

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (Rev. 2/95)

1- File Copy

Office Action Summary	Application No. 08/817,704	Applicant(s) Swaak, A. J.
	Examiner Thomas Cunningham	Group Art Unit 1644

☒ Responsive to communication(s) filed on *May 21, 1999*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *14-26* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *14-26* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *5*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. The request filed on 5/21/99 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/817,704 is acceptable and a CPA has been established. An action on the CPA follows. Claims 14-26 are active.

2. Claims 18, 19, 23 and 24 are rejected under 35 U.S.C. 112, second paragraph as being vague and indefinite as to the scope of the phrase "symptoms associated with rheumatoid arthritis". Does this language limit the claim to treatment of patients having arthritis? Is the method intended to embrace treatment of anemia? In the absence of clarification this language must be interpreted broadly as encompassing treatment of any disease that shares a symptom with arthritis. E.g. any disease that produces pain, swelling or inflammation.

3. Claims 20, 25 and 26 are rejected under 35 U.S.C. 112, second paragraph as being vague and indefinite as to the scope of the phrase "disease activity of rheumatoid arthritis". Does this language limit the claim to treatment of patients having arthritis? Is the method intended to embrace treatment of anemia? In the absence of clarification this language must be interpreted broadly as encompassing treatment of any disease that shares an activity with arthritis. E.g. any disease that produces pain, swelling or inflammation.

4. Claims 14-26 are rejected under 35 U.S.C. 112, first paragraph as lacking adequate enablement. Claims 14-26 are directed to methods of treating chronic inflammation, and autoimmune diseases such as arthritis using erythropoietin or erythropoietin fragments, derivatives or mutants.

A. Inflammatory Diseases, scope. One with skill in the art would not expect to be able to use erythropoietin products to treat chronic inflammatory diseases in general. Erythropoietin is a humoral regulator of erythropoiesis and stimulates the production of erythrocytes. It is used to treat diseases associated with anemia in order to increase the production of red blood cells. Pages 4-5 of the specification speculate that erythropoietin may exert anti-inflammatory effects either by mobilizing iron to hemoglobin production and away production of hydroxy-radicals associated with tissue damage in diseases like arthritis. Another suggested mechanism is the role EPO may have on Th1/Th2 balance and on particular cytokines.

The study described in the specification indicates that EPO treatment of subjects with chronic anemia associated with rheumatoid arthritis ("anemia of chronic disease":ACD) resulted in certain clinical improvements, including reductions in pain score and morning stiffness and improvement in well-being.

One with skill in the art would not have had a reasonable expectation of treating diseases other than ACD (or RA) using EPO because of the complexity of the physiological mechanisms of different autoimmune diseases. Phenomena such as abnormal iron or cytokine levels associated with ACD would not reasonably be expected to occur in other autoimmune or inflammatory diseases. Robbins, Pathological Basis of Disease, page 190 indicated that "Although it would be attractive to explain all autoimmune diseases by a single mechanism, it is now clear there are a number of ways by which tolerance can be bypassed" and defects associated with autoimmune diseases differ from one disorder to another. Therefore, it would have been unpredictable whether treatment of subjects having other autoimmune or inflammatory disorders with EPO would result in clinical improvement.

--The instant claims are limited to methods of "treating chronic inflammation" (see independent claim 14), methods of "treating symptoms associated with rheumatoid arthritis (see independent claim 18) or methods of "ameliorating a disease activity of rheumatoid arthritis" (see independent claim 20). Most diseases as well as surgical procedures are associated with inflammation. The specification indicates that administration of EPO results in reductions in pain, morning stiffness and well-being for arthritis patients, but does not evidence that EPO treats other chronic inflammatory diseases. Applicant need not evidence that every possible inflammatory disease may be treated by EPO in order to support a generic claim, see In re Cook and Merigold, 169 USPQ

298 (CCPA 1971) and In re Cavallito and Gray, 127 USPQ 202 (CCPA 1960). However, evidence that a reasonable number of species of chronic inflammatory diseases are treatable with EPO would obviate this rejection. Additionally, this rejection will be dropped for claims 18-20 and 23-26 if these claims are intended to be limited to treatment of patients having arthritis.

B. (Moot) Fragments, derivatives, mutants. One with skill in the art would not be able to identify without undue experimentation erythropoietin fragments or variants without some indication of the desired functional activity (e.g. scavenging iron, modulating cytokine levels, etc) and some indication of conserved structure. It would be necessary to determine all the known and unknown functional activities of erythropoietin and then to determine which compounds had similar activities. According to Smilek et al., PNAS even minor changes in the structure of a biologically active molecule can have drastic effects on functional activity. It would require undue experimentation to determine which erythropoietin derivatives or mutants would retain the desired functional activities. Applicant's attention is directed to Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016 (CAFC 1991):

> Patent applicant is entitled to claim invention generically, if invention is described sufficiently to meet requirements of 35 USC 112; however, applicant, in claims for DNA sequences encoding erythropoietin, which has claimed every possible analog of gene containing about 4,000 nucleotides, but which has provided details for preparing only few EPO analog genes has not provided sufficient disclosure to support its claims, since, in view of structural complexity of EPO gene, manifold possibilities for change in its structure, and uncertainty as to what utility will be possessed by these analogs, additional disclosure is needed as to identifying various analogs within scope of claim, methods for making them, and structural requirements for producing compounds with EPO-like activity.

While Amgen addresses the unpredictability of which DNA sequences would encode functional erythropoietin analogs, the same or similar issues of unpredictability of the functional characteristics of analogs of erythropoietin are pertain to whether the claims in the instant application are enabled. Applicant urges on page 6 of the last response that so long as the recited erythropoietin products meet two criteria--that they are nonimmunogenic and ameliorate inflammation--they may be used in the present invention. However, the specification provides no guidance as to which of billions of different possible analogs or fragments would meet these two criteria.

--Issue B is moot because the claim language has been amended to exclude fragments and muteins of EPO.

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 14-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over GB 2 171 304 A (published 28 August 1986). Claims 14-26 all embrace treatment of patients having ACD "the anemia of rheumatoid arthritis" with EPO. ACD is a chronic inflammatory disease, it has symptoms associated with RA and exhibits a disease activity of RA.

The cited patent discloses treatment of the anemia of RA using human EPO. Human EPO would be nonimmunogenic when administered to humans because it is a "self" protein and would not be recognized as foreign by the human immune system.

The cited prior art patent provides general direction as to how to optimize dosage and frequency of EPO administration, see page 2, lines 23-25. It explicitly suggests treatment of ACD patients by daily doses of EPO over a week. It does not *explicitly* suggest treatment over a period of two weeks as is now required by the instant claims.

One with ordinary skill in the medical arts would be able to routinely optimize the dosage,

frequency of administration and duration of EPO treatment for ACD by merely observing the "condition of the patients" and determining duration of treatment accordingly. Therefore, the instant claims are prima facie obvious over the cited art.

--The Applicant urges that the cited patent does not teach using EPO to treat inflammation, morning stiffness, painful and swollen joints, pain or a loss of grip strength. However, the claims are not limited to patients manifesting just these symptoms and read on the prior art ACD patients. The claims do not exclude treatment of ACD or RA patients with EPO as is taught by the prior art. Limitation of the claims to exclude treatment of ACD or RA patients with EPO would obviate this rejection.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thomas M. Cunningham, Ph.D, J.D. whose telephone number is (703) 308-3968. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

TC

THOMAS M. CUNNINGHAM
PRIMARY EXAMINER
GROUP 1800